



## CASE REPORT

# Long-term control of refractory Schnitzler syndrome with anakinra: a case report

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## KEYWORDS

Anakinra  
Schnitzler syndrome

## ABSTRACT

Schnitzler syndrome is a rare inflammatory disorder characterized by chronic urticarial rash, monoclonal gammopathy, periodic fever, arthralgia/arthritis and bone pain. However, the results of management of Schnitzler syndrome are often disappointing and its treatment remains a challenge. No cases of spontaneous complete remission have been reported. Anakinra is an interleukin 1 receptor antagonist used for the treatment of rheumatoid arthritis, and has been reported to be universally effective for Schnitzler syndrome. Here, we report the first Asian patient with Schnitzler syndrome who achieved long-term control with anakinra, after previous failures with various therapeutic approaches.

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## Introduction

Schnitzler syndrome was first described in 1972 by the French dermatologist, Schnitzler.<sup>1</sup> It is a rare disabling disorder diagnosed on the basis of a chronic urticarial rash and a monoclonal immunoglobulin M (IgM) gammopathy, accompanied by at least two of the following features: intermittent unexplained fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepatosplenomegaly, elevated erythrocyte sedimentation rate or leukocytosis, and abnormal findings on bone morphologic investigations.<sup>2</sup> Treatment is often difficult and no universally effective treatment is currently available. Here we report the first Asian patient with Schnitzler syndrome who achieved satisfactory long-term control with anakinra.

## Case report

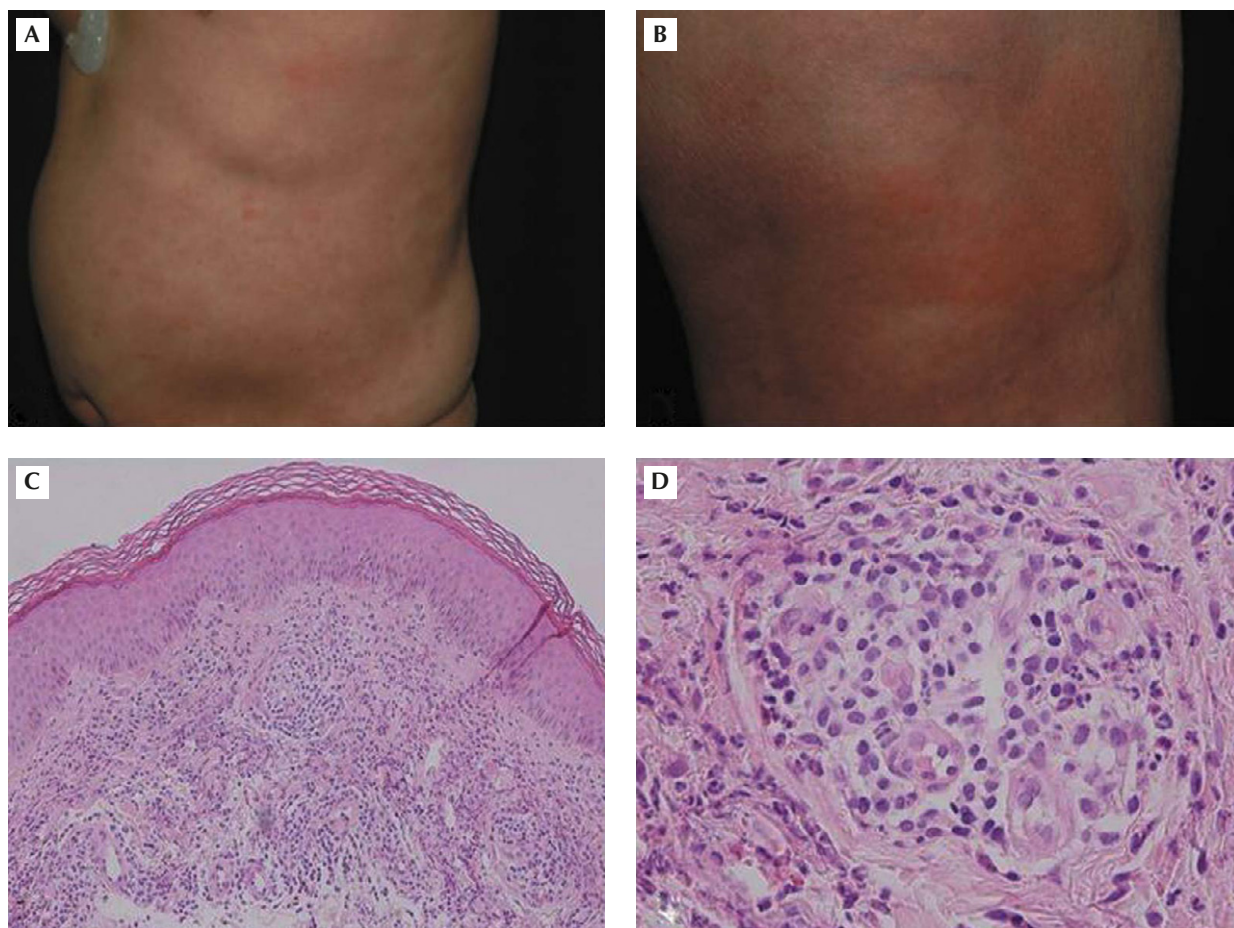
A 64-year-old male with a past history of arrhythmia was referred to our outpatient clinic in 2007. He presented with

a 3-year history of an intermittent, widespread, non-pruritic urticarial rash. The urticarial rash lasted from several hours to more than a day. He had been diagnosed with chronic urticaria by several dermatologists since 2004. The symptoms were resistant to different antihistamines but could be partially controlled with oral corticosteroids. Two years after the onset of these symptoms, intermittent fever (peaks over 39°C) with chills, malaise, muscle soreness and polyarthralgia were detected. He presented at our dermatology clinic in November 2007. Physical examination revealed numerous variously sized, irregularly-shaped wheals on the trunk, and upper and lower extremities (Figures 1A and 1B). The rash was not triggered by any precipitating factors. Neither hepatosplenomegaly nor palpable lymph nodes were noted. Laboratory tests revealed an increased erythrocyte sedimentation rate (ESR) ( $>110$  mm/h, normal  $<20$ ), anemia (hemoglobin 112 g/L), leukocytosis (white cell count  $14.27 \times 10^3/\mu\text{L}$  with  $10.8 \times 10^3/\mu\text{L}$  neutrophils), and platelet count  $335 \times 10^3/\mu\text{L}$ . Biochemical investigation revealed increased ferritin (1025 pmol/L, normal 59.8–847 pmol/L) with decreased iron (10.4  $\mu\text{mol/L}$ , normal 13.4–31.9  $\mu\text{mol/L}$ ) and total iron-binding capacity (37.6  $\mu\text{mol/L}$ , normal 49.2–59.4  $\mu\text{mol/L}$ ). Complement levels (C3 1.61 g/L, normal 0.816–1.814 g/L; C4 0.131 g/L, normal  $0.275 \pm 0.107$  g/L) and fibrinogen (9.86  $\mu\text{mol/L}$ , normal 4.81–10.64  $\mu\text{mol/L}$ ) were normal. Tumor necrosis factor (TNF)- $\alpha$  (8.93 pg/mL, normal  $<8.1$  pg/mL) and  $\beta$ -2

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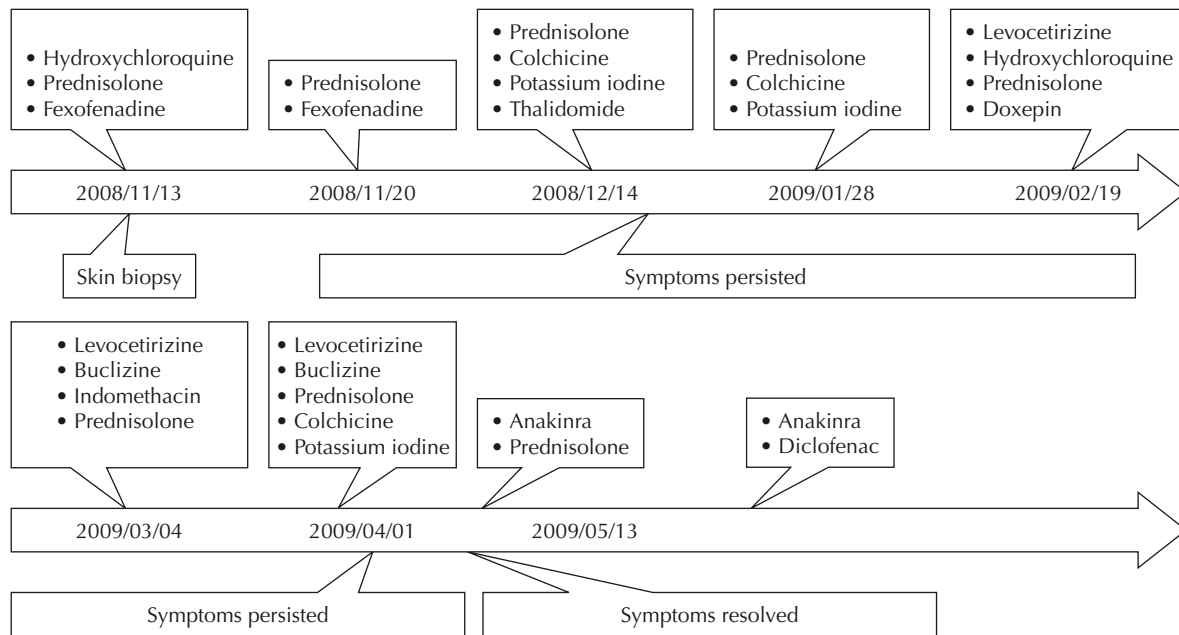


**Figure 1** (A,B) Many non-pruritic, irregularly shaped, erythematous, edematous wheals, mainly on the trunk and extremities. (C,D) Histologic examinations revealed perivascular and interstitial neutrophilic and lymphocytic infiltration in the superficial dermis (H&E, 200x, 400x, respectively).

microglobulin levels (2.3 mg/L, normal 0.7–1.8 mg/L) were slightly increased. Serum protein electrophoresis showed increased alpha-1 and alpha-2 globulins, and a small paraprotein peak in the gamma region. The IgM level was 1250 mg/L (normal range, 1605.7±722 mg/L), the IgG level was 21.80 g/L (normal range, 14.20±27.98 g/L) and the IgA level was 4700 mg/L (normal range, 2593.4±828.4 mg/L). Serum immunofixation electrophoresis study revealed a thin band of IgM/kappa monoclonal gammopathy. A small amount of kappa chain Bence-Jones protein was found in urine by immunofixation electrophoresis. Antinuclear antibodies, rheumatoid factor and cryoglobulins were all negative. Hepatitis B and C were excluded by serologic examinations. Biopsy of affected skin demonstrated perivascular and interstitial neutrophilic infiltration in the upper dermis. Bone marrow biopsy showed erythroid hyperplasia without malignant cells. A computed tomographic scan of the chest, abdomen and pelvis was negative for proliferative disorders. Bone scintigraphy showed increased uptake in the lower cervical, upper thoracic and lower lumbar spines, the right acromion, and the right anterior sixth rib.

Based on the symptoms and results, which included chronic urticaria, monoclonal gammopathy, fever, arthralgia, bone

pain and elevated erythrocyte sedimentation rate, a diagnosis of Schnitzler syndrome was made. The patient was initially treated with prednisolone (10 mg/day), colchicine (1 mg/day), potassium iodine (900 mg/day), hydroxychloroquine (800 mg/day), indomethacin (75 mg/day), fexofenadine (120 mg/day), levocetirizine (5 mg/day), doxepin (50 mg/day), and buclizine (25 mg/day), either alone or in combination, but no significant improvement was noted (Figure 2). A trial of thalidomide (100 mg/day) had to be stopped because of severe drowsiness. Six months after the diagnosis of Schnitzler syndrome, the patient was commenced on subcutaneous anakinra (100 mg/day) with diclofenac (100 mg/day). The urticarial lesions and fever had completely disappeared within 10 hours of the first injection, and the bone pain, arthralgia and malaise had disappeared within 1–2 days. Hemoglobin, white cell count, serum iron and ferritin, serum IgG and IgA levels normalized; the ESR was reduced and returned to normal (ESR 1h, 17 mm/h). The IgM monoclonal gammopathy persisted, but paraprotein fell from 972 mg/dL to 429 mg/dL. No Bence-Jones protein was found in the urine (Table 1). The patient remained symptom-free at 11 months, having taken no oral corticosteroids over the same period.



**Figure 2** Treatment course of the patient.

**Table 1** Results of laboratory investigations.

Laboratory investigations	Pre-anakinra	Post-anakinra
ESR (mm/h, 1 hr)	>110	17
WBC ( $\times 10^9/L$ )	14.27	6.48
Hemoglobin (g/L)	112	130
Ferritin (pmol/L)	1025	308
Iron ( $\mu\text{mol/L}$ )	10.4	17.7
TIBC ( $\mu\text{mol/L}$ )	37.6	44.8
Urine IFE	Bence-Jones protein (+)	Bence-Jones protein (–)
IgG (g/L)	21.8	14.1
IgM (mg/L)	1250	2510
IgA (mg/L)	4700	2260
Serum IFE	IgM/kappa monoclonal gammopathy (+)	IgM/kappa monoclonal gammopathy (+)
TNF- $\alpha$ (pg/mL)	8.93	NA
C3/C4 (g/L)	1.61/0.13	NA
$\beta$ -2 microglobulin (mg/L)	2.3	NA

ESR=erythrocyte sedimentation rate; WBC=white blood count; TIBC=total iron-binding capacity; IFE=immunofixation electrophoresis; Ig=immunoglobulin; TNF=tumor necrosis factor; NA=not available; C3/C4=complement component C3/C4.

urticaria and arthralgia/arthritis. The main clinicopathologic differential diagnosis consists of a group of diseases characterized by neutrophilic urticarial dermatosis with systemic diseases, namely adult-onset Still's disease, lupus erythematosus and hereditary autoinflammatory fever syndrome. Schnitzler syndrome is also characterized by monoclonal gammopathy, periodic fever and bone pain, but its precise pathogenesis remains unclear. Some studies<sup>3,4</sup> have reported IgM deposits around the superficial dermal vessels, within the superficial dermis and along the dermal-epidermal junction. Lipsker et al<sup>4</sup> revealed the presence of anti-skin IgM autoantibody, with the same isotype as circulating monoclonal immunoglobulins, in some patients, and suggested that in situ IgM-mediated complement activation and subsequent tissue damage was responsible for the skin manifestations of Schnitzler syndrome. However, these IgM depositions could only be detected in 25% of patients with Schnitzler syndrome. In another study,<sup>5</sup> a patient with Schnitzler syndrome received the anti-CD20 antibody rituximab for 5 weeks, resulting in decreased peripheral B-cell counts and IgM levels, though the urticarial lesions, fatigue and bone pain persisted. Polyclonal increases in IgA and IgG levels had been documented in two case reports.<sup>6,7</sup> Moreover, IgA monoclonal gammopathy has been reported in Schnitzler syndrome.<sup>8</sup> It has been suggested that anti-interleukin (IL)1 $\alpha$  IgA autoantibodies are more frequent in Schnitzler's syndrome than in controls.<sup>7</sup> However, the role of these monoclonal or polyclonal paraproteins have not been fully established. It is still unclear if the monoclonal paraprotein or elevated immunoglobulin is causative in nature, or simply a result of continuous antigenic stimulation. Further studies are needed to investigate the role of monoclonal gammopathy in Schnitzler syndrome.

## Discussion

Schnitzler syndrome is a rare inflammatory disorder of unknown pathophysiology, presenting as chronic refractory



The role of cytokines in Schnitzler syndrome has not been fully established. In a study by de Kleijn et al,<sup>9</sup> only slight elevations of IL-6 were observed in one patient with Schnitzler syndrome, and no increases in circulating levels of IL-1 $\beta$  or TNF $\alpha$  were found. Normal plasma IL-1 levels have also been observed in other cases.<sup>10,11</sup> One study,<sup>12</sup> however, has proposed that uncontrolled activation of IL-1 $\alpha$  plays an important role in the pathophysiology of Schnitzler syndrome. Saurat et al<sup>12</sup> found remarkably increased IgG-type autoantibody directed against IL-1 $\alpha$  in the serum of six out of nine patients with Schnitzler syndrome. They postulated that anti-IL-1 $\alpha$  IgG could prolong the half life of IL-1 $\alpha$ , change its tissue distribution, and enhance its effects,<sup>12</sup> which might account for some of the symptoms and signs of Schnitzler syndrome. However, it has not been found in all patients with Schnitzler syndrome, and was detected in 18% of healthy individuals.<sup>13</sup>

Treatment of Schnitzler syndrome remains a challenge, although many therapeutic approaches, including glucocorticosteroids, non-steroidal anti-inflammatory drugs, colchicine, dapsone, thalidomide, interferon- $\alpha$ , rituximab, immunoglobulins, methotrexate, cyclophosphamide, purine analogs, plasma exchange and photochemotherapy have all been described in the literature. The symptoms and signs in these patients were usually partially responsive to oral corticosteroids, but long-term, high-dose therapy was required to achieve effective control. Scharz et al<sup>14</sup> successfully treated a Schnitzler syndrome patient with interferon- $\alpha$  and suggested that it might induce high circulating levels of IL-1 receptor antagonists in humans.

Anakinra, a recombinant form of IL-1 receptor antagonist, competitively inhibits the binding of IL-1 $\alpha$  and IL-1 $\beta$  to the IL-1 receptor. Rheumatologists and pediatricians have successfully used it to treat rheumatoid arthritis and autoinflammatory diseases such as Muckle-Wells syndrome, TNF-associated periodic syndrome, and hyper-IgD syndrome.<sup>5</sup> Because of the clinical similarities between Schnitzler syndrome and some autoinflammatory diseases with increased IL-1 production that were effectively treated with anakinra, anakinra has been used for the management of Schnitzler syndrome in many studies. Ryan et al<sup>15</sup> examined the ex vivo production of cytokines and the effects of inhibition of IL-1 in Schnitzler syndrome. The IL-1 inhibitor, IL-trap, and the caspase-inhibitor, YVAD, significantly reduced the hypersecretion of IL-1, IL-6 and TNF, which was correlated with clinical remission.

To date, 17 cases with excellent responses to anakinra have been reported.<sup>3,5-7,10,15-23</sup> All the reported cases, however, have been Caucasians, and no Asian cases have been reported. Most of the patients had failed various other treatment regimens before initiation of anakinra therapy. Remission of fever, and skin rash was always induced within 24 hours of anakinra treatment at 100 mg/day. In some of these patients, bone pain and arthralgia took days to weeks to resolve. The symptoms recurred within 24–48 hours when

anakinra was discontinued, but usually disappeared again after resumption of treatment,<sup>3,10,17,18</sup> as noted in our patient. Signs of systemic inflammation, such as elevated ESR, C-reactive protein, ferritin and leukocytosis were observed in patients with Schnitzler syndrome; these remained increased throughout the course of the disease, peaking during exacerbation. These serologic parameters were usually reduced and normalized after anakinra treatment. The longest follow-up period in a patient continuously treated with anakinra was 21 months.<sup>17</sup> The only recorded adverse effect of anakinra is painful erythematous eruption at the injection site, which occurred in three out of these 17 patients.<sup>3,6,18</sup> Despite the therapeutic effects of anakinra, long-term follow-up is warranted because 15% of patients with Schnitzler syndrome go on to develop lymphoproliferative disorders within 10–20 years.<sup>24</sup>

Schnitzler syndrome is a rare cause of chronic urticaria and may be complicated by subsequent lymphoproliferative disorders and systemic amyloidosis.<sup>8</sup> In cases of chronic refractory urticaria, serum protein electrophoresis can be performed to rule out the possibility of Schnitzler syndrome. The prompt and dramatic response in our patient, as well as in other reports, suggests that anakinra might be a promising and effective option for the treatment of Schnitzler syndrome. It also underlines the pivotal role of IL-1 in the pathogenesis of Schnitzler syndrome. However, further long-term studies are warranted to determine if anakinra can reduce the incidences of lymphoproliferative diseases and amyloidosis in patients with Schnitzler syndrome.

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